COMMONWEALTH OF AUSTRALIA

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Warning

CHARLES DARWIN UNIVERSITY

Family Name	
Given Names	
Student Number	
Teaching Period	Semester 2, 2015

FINAL EXAMINATION	**DURATION**
PHA214 – Biotechnology and Pharmacogenomics	Reading Time: **10** minutes Writing Time: **120** minutes

INSTRUCTIONS TO CANDIDATES

1.1 The examination has 2 sections

Section A:
Suggested Time: 50 mins — Multiple Choice Questions: Answer ALL (40) questions
Marks: 50 Marks

Section B:
Suggested Time: 70 mins — Short Answer Questions: Answer ALL questions
Marks: 68 Marks

Section A must be answered on the Answer sheet provided and must be handed in with your answer booklet. Please ensure that your name and student number are clearly indicated on your Answer Sheet and at the top of this examination paper.
Section B is to be answered in separate booklets.

1.2 Note that questions ARE NOT of equal value.

1.3 Read ALL questions carefully.

1.4 Do not commence writing until instructed to do so.

EXAM CONDITIONS

This is a CLOSED BOOK examination
Any non-programmable calculator is permitted
No handwritten notes are permitted
No dictionaries are permitted
Answer on the supplied examination material/s only

ADDITIONAL AUTHORISED MATERIALS	EXAMINATION MATERIALS TO BE SUPPLIED
No additional printed material is permitted	1 x 16 Page Book Faculty/School Multiple Choice Answer Sheet

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Section A
Multiple Choice Questions
Total Number of Marks for this section: Forty (40)

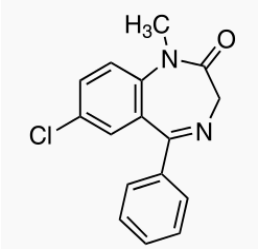
This section should be answered on the Answer Sheet provided.
Each question is worth one (1) mark as indicated.
Suggested time allocation for Section A: 50 mins

Section B
Total Number of Marks for this section: Sixty eight (68)

This section should be answered in the Booklet provided.
Each question is worth the number of marks indicated.
Please answer all parts (a-d) for all questions.
Suggested time allocation for Section B: 70 mins

Question 1

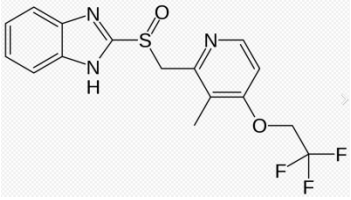
a. The diagram below shows the structure of diazepam ($C_{16}H_{13}ClN_2O$), a muscle relaxant and a sedative. Diazepam binds to benzodiazepine receptors which mediate sleep and affects muscle relaxation.



Redraw the structure in your answer paper and label all the possible binding interactions that can take place in the binding site between diazepam molecule and the amino acid residues of the protein involved.

[3 marks]

b. Following is the structure of Lansoprazole ($C_{16}H_{14}F_3N_3O_2S$), a proton-pump inhibitor drug molecule (*logP* = 3.03).



i) State the rules in 'Lipinski-Rule of Five'

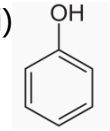
ii) Calculate the properties of the molecule relating to 'Lipinski-Rule of Five'. State whether the molecule is drugable and explain your answer.

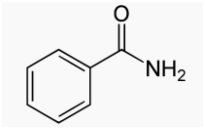
[4 marks]

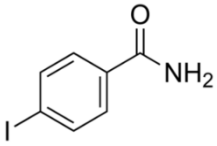
Question 2

a. Calculate the log*P* value for the 3 structures shown below and arrange them in the order of increasing hydrophobicity.

[log*P* for benzene = 2.13; π(OH) -0.67; π(I)= 1.12; π($CONH_2$)= - 1.49]

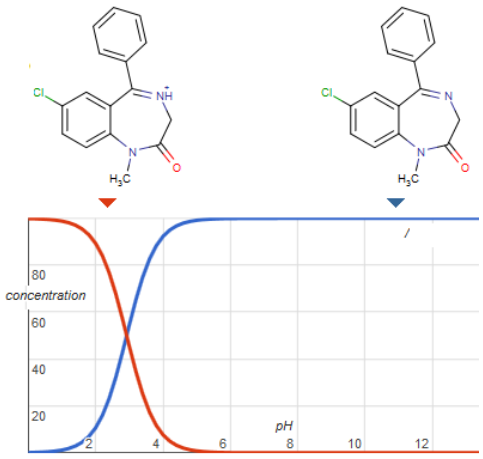
i) 

ii) 

iii) 

[4 marks]

b. The graph below represents a plot of %concentration versus pH of diazepam. Diazepam's pKa = 2.92 and log P = 3.08.



i) What does the log P value indicate about the nature of the molecule?

ii) Discuss the nature of the major species at pH 7.4.

[3 marks]

Question 3

A new drug has been developing to treat prostate cancer. This drug is design to be taken orally every day during the treatment period, and it inhibits the growth of the cancer cell. During the initial clinical trial, it is found that 20% of the studies population has a very low blood concentration of the drug. Briefly outline THREE (3) possible mechanism of genetic variation that can explain this observation.

[3 marks]

Question 4

The '*genome-wide association study*' and the '*candidate gene study*' are the two primary approaches to genetic studies. In a short paragraph, briefly compare how the concepts can be useful for pharmacogenetics researches.

[5 marks]

Question 5

Antipsychotics are a group of medication that commonly used in a wide range of mental illness. However, the treatment outcome from this group of drug is always unpredictable. A recent study (include 593 subjects) investigates the pharmacogenetic of these drugs (olanzapine, risperidone, quetiapine and perphenazine) comparing their efficacy and adverse effect. The study's finding is summarised in the following table.

	Genotype 1		Genotype 2		Genotype 3	
Olanzapine	↑↑↑↑	↑	↓	↓↓	↑↑	↑↑
Risperidone	↑↑	↑↑	--	--	↑	↓↓↓
Quetiapine	--	↓	↑	↑	--	↓↓↓
Perphenazine	↓	↓↓	↑↑↑↑	↑↑	↑↑	↑

	Antipsychotic effect
	Adverse effect

Each ↑ indicate a factor increase in efficacy (or adverse effect);

Each ↓ indicate a factor reduce in efficacy (or adverse effect);

-- indicate the effect is similar to the average

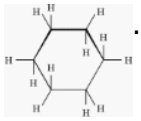
a. Comment on the finding of this study.

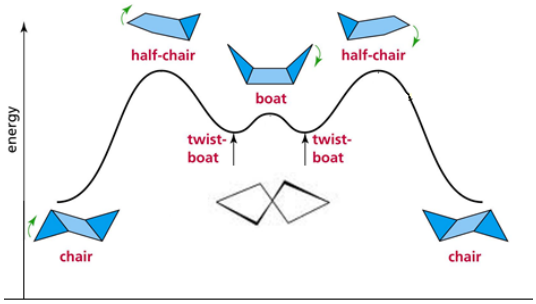
[5 marks]

b. If a patient is found to carry genotype 3, which antipsychotic drug will you recommend? Justify your answer.

[5 marks]

Question 6

a. The 3 dimensional structure of Cyclohexane (C_6H_{12}) is not the regular hexagon  . It has several possible 3d conformations as shown below.



Based on the energy profile diagram given above, answer the following questions.

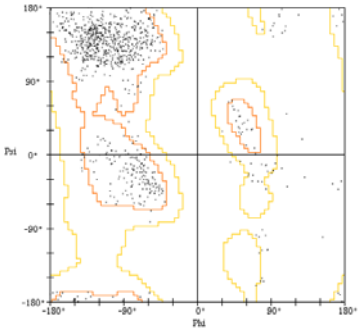
i) What is the 3d structure of the most stable conformation of cyclohexane? Why?

ii) What do the twist boat conformations of cyclohexane represent? Why?

iii) What do the half-chair conformations of cyclohexane indicate? Why?

[3 marks]

b. In reference to the figure below, discuss the significance of Ramachandran plot in homology modeling of proteins.



[2 marks]

c. The Hammet constant **(**σ) for -OH substituent, if attached to a benzoic acid (C_6H_5COOH) molecule is as follows:

σ_m of -OH = 0.12

σ_p of -OH = -0.37

Where would you attach the –OH group to the benzene ring to make benzoic acid a stronger acid? Explain your answer.

[2 marks]

Question 7

Explain the role of phase I, phase II and phase III reactions in drug metabolism and provide an example of each.

[9 marks]

Question 8

Explain the role UDP-glucuronosyltransferase plays in bladder carcinogenesis.

[5 marks]

Question 9

Fentanyl is a synthetic opioid analgesic used for chronic pain management in cancer patients. Fentanyl is 50 to 100 times more potent than morphine and may be administrated intravenously, transdermally and transmucosally. Due to its lipophilicity and low molecular weight, fentanyl is readily absorbed through the skin. The amount of fentanyl released from patch transdermal system is proportional to the surface area of the patch, with four doses/sizes available. Fentanyl is metabolised to norfentanyl, being the major metabolite. The CYP3A subfamilies are the most abundant isozymes and have been shown to mediate the dealkylation of fentanyl to norfentanyl in the liver and intestinal epithelium in humans. Using the below information, comment on fentanyl metabolism and toxicity.

Case	Sex	Age	Genotype CYP3A4*1	Genotype CYP3A5*3	Fentanyl (μg/L)	Norfentanyl (μg/L)
1	F	32	HM↓↓	HM↓↓	59.0↑↑↑↑	3.9
2	F	44	HT↓	HT↓	19.0↑↑	7.6
4	F	87	WT	HM↓↓	1.7↑	2.9
12	F	46	WT	HM↓↓	7.8↑	11.0
16	M	48	WT	HM↓↓	16.0↑	27.0
23	M	24	HT↓	WT	21.0↑↑	10.5
24	M	29	HT↓	HM↓↓	32.0↑↑↑	2.5
25	F	38	WT	WT	0.5	11.0

Where HM is homozygous, HT is heterozygous, WT is wild type

[6 marks]

Question 10

How can a specific gene, such as the β-globin gene, be isolated from cDNA library?

[5 marks]

Question 11

No gene therapy has yet been approved for general use. What are the current limitations of this technology?

[4 marks]